PHARMACOVIGILANCE PLAN FOR

EMERGENCY USE AUTHORIZATION # 27034

OF

PFIZER-BIONTECH COVID-19 VACCINE

Date of Report: 05-DECEMBER-2020

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LIST OF ABBREVIATIONS

Abbreviation	Definition of Term
AE	adverse event
A:G	albumin:globulin
BMI	body mass index
COVID-19	coronavirus disease 2019
CSR	clinical study report
CT	clinical trial
DART	developmental and reproductive toxicology
DCA	data capture aid
DLP	data-lock point
ECDC	European Center for Disease Control
ED	emergency department
EEA	European Economic Area
EUA	emergency use authorization
EU	European Union
FDA	(US) Food and Drug Administration
GLP	good laboratory practice
HBV	hepatitis b virus
HCV	hepatitis c virus
HIV	human immunodeficiency virus
IA	interim analysis
ICU	intensive care unit
IM	intramuscular(ly)
IND	investigational new drug
LNP	lipid nanoparticle
MAH	marketing authorization holder
mRNA	messenger ribonucleic acid
modRNA	nucleoside-modified messenger ribonucleic acid
NDA	new drug application
NHP	nonhuman primate
PK	pharmacokinetic
PVP	pharmacovigilance plan
RBC	red blood cell
RNA	ribonucleic acid
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
siRNA	small-interfering RNA
TESSy	The European Surveillance System
UK	United Kingdom
US	United States
V8	variant 8
V9	variant 9
VAED	vaccine-associated enhanced disease

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Abbreviation	Definition of Term
VAERD	vaccine-associated enhanced respiratory disease
WBC	white blood cells
WHO	World Health Organization

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1. INTRODUCTION

Product Details

Table 1. Product Details[a]

Product	Pfizer-BioNTech COVID-19 vaccine is a nucleoside-modRNA encoding the viral spike glycoprotein S of SARS-CoV-2.
Brief description of the product	Chemical class: Nucleoside-modRNA encapsulated in LNP. Mechanism of Action: The LNP enables entry into host cells and expression of the S protein. The vaccine elicits both antibody and cellular immune responses to the viral spike glycoprotein S, which are known to contribute to the mechanism of protection. Important information about its composition: The Pfizer-BioNTech COVID-19 vaccine: • is a white to off-white, sterile, preservative-free, frozen suspension; • it contains a modRNA encoding S protein of SARS-CoV-2; • also includes the following inactive ingredients: lipids ((4 hydroxybutyl) azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 2 [(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 1,2-distearoyl-sn-glycero-3-phosphocholine, and cholesterol), potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dihydrate, and sucrose.
Indication	Proposed: Prevention of COVID-19 in individuals 16 years of age and older.
Dosage and route of administration	Proposed: Series of two doses (0.3 mL each) 21 days apart, IM administered.

a. Pfizer-BioNTech COVID-19 vaccine Full EUA Prescribing Information (Module 1.14)

Data Lock Point: 14 November 2020 (Pfizer Clinical Database)
02 October 2020 (BioNTech Clinical Database)

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2. SAFETY SPECIFICATION

Elements of the Safety Specification

2.1.1. Non-Clinical

Nonclinical evaluation of BNT162b2 included pharmacology (mouse immunogenicity and NHP immunogenicity and challenge studies), pharmacokinetic (series of biodistribution, metabolism and pharmacokinetic studies), and toxicity (2 GLP rat repeat-dose toxicity) studies in vitro and in vivo. A DART study is ongoing in rats. No additional toxicity studies are planned for BNT162b2.

Nonclinical studies in mice and NHP for BNT162b2 (Pfizer-BioNTech COVID-19 vaccine) demonstrated both a strong neutralizing antibody response and a Th1-type $CD4^+$ and an $IFN\gamma^+$ $CD8^+$ T-cell response. The Th1 profile is characterized by a strong IFNγ, but not IL-4, response indicating the absence of a potentially deleterious Th2 immune response and is a pattern favored for vaccine safety and efficacy.[1] Rhesus macaques (Study VR-VRT-10671) that had received two IM immunizations with 100 µg BNT162b2 or saline 21 days apart were challenged with 1.05×10^6 plaque forming units of SARS-CoV-2 (strain USA-WA1/2020), split equally between the intranasal and intratracheal routes.[2] BNT162b2 provided complete protection in the lungs compared to the saline control with no clinical, radiological or histopathological evidence of vaccine-elicited disease enhancement.

An intravenous rat PK study, using an LNP with the identical lipid composition as Pfizer-BioNTech COVID-19 vaccine, demonstrated that the novel lipid excipients in the LNP formulation, ALC-0315 and ALC-0159, distribute from the plasma to the liver. While there was no detectable excretion of either lipid in the urine, the percent of dose excreted unchanged in feces was ~1% for ALC-0315 and ~50% for ALC-0159. Further studies indicated metabolism played a role in the elimination of ALC-0315. Biodistribution was assessed using luciferase expression as a surrogate reporter formulated like Pfizer-BioNTech COVID-19 vaccine, with the identical lipid composition. After IM injection of the LNP-formulated RNA encoding luciferase in BALB/c mice, luciferase protein expression was demonstrated at the site of injection 6 hours post dose and was not detected after 9 days. Luciferase was detected to a lesser extent in the liver; expression was present at 6 hours after injection and was not detected by 48 hours after injection. After IM administration of a radiolabeled LNP-mRNA formulation containing ALC-0315 and ALC-0159 to rats, the percent of administered dose was also greatest at the injection site. Outside of the injection site, total recovery of radioactivity was greatest in the liver and much lower in the spleen, with very little recovery in the adrenal glands and ovaries. The metabolism of ALC-0315 and ALC-0159 was evaluated in blood, liver microsomes, S9 fractions, and hepatocytes from mice, rats, monkeys, and humans. The in vivo metabolism was examined in rat plasma, urine, feces, and liver samples from the PK study. ALC-0315 and ALC-0159 are metabolized by hydrolytic metabolism of the ester and amide functionalities, respectively, and this hydrolytic metabolism is observed across the species evaluated.

In GLP toxicity studies, two variants of the Pfizer-BioNTech COVID-19 vaccine candidate were tested, designated “variant 8” and “variant 9” (V8 and V9, respectively). The variants differ only in their codon optimization sequences which are designed to improve antigen

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expression, otherwise the amino acid sequences of the encoded antigens are identical. Pfizer-BioNTech COVID-19 vaccine (V9) was evaluated clinically and submitted for application. Two GLP-compliant repeat-dose toxicity studies were performed in Wistar Han rats; one with each variant. Both studies were 17 days in duration with a 3-week recovery period. A DART study in Wistar Han rats is ongoing. Safety pharmacology, genotoxicity and carcinogenicity studies have not been conducted, in accordance with the 2005 WHO vaccine guideline.[3]

The IM route of exposure was selected for nonclinical investigation as it is the clinical route of administration. Rats were selected as the toxicology test species as they demonstrated an antigen-specific immune response to the vaccine and are routinely used for regulatory toxicity studies with an extensive historical safety database.

Administration of up to 100 µg Pfizer-BioNTech COVID-19 vaccine by IM injection to male and female Wistar Han rats once every week, for a total of 3 doses, was tolerated without evidence of systemic toxicity. Expected inflammatory responses to the vaccine were evident such as edema and erythema at the injection sites, transient elevation in body temperature, elevations in WBC and acute phase reactants, and lower A:G ratios. Injection site reactions were common in all vaccine-administered animals and were greater after boost immunizations. Changes secondary to inflammation included slight and transient reduction in body weights and transient reduction in reticulocytes, platelets and RBC mass parameters. Decreased reticulocytes were observed in rats treated with the licensed LNP-siRNA pharmaceutical Onpattro™ (NDA # 210922) but have not been observed in humans treated with this biotherapeutic [4] suggesting this is a species-specific effect. Decreased platelet counts were noted after repeat administration, but were small in magnitude of change, likely related to inflammation-related platelet activation and consumption, and unassociated with other alterations in hemostasis. Elevated levels of gamma-glutamyl transferase were observed in the first repeat-dose toxicity study with Pfizer-BioNTech COVID-19 vaccine (V8) without evidence of cholestasis or hepatobiliary injury but was not recapitulated in the second repeat dose-toxicity study with Pfizer-BioNTech COVID-19 vaccine (V9), the final clinical candidate. All changes in clinical pathology parameters and acute phase proteins were reversed at the end of the recovery phase for Pfizer-BioNTech COVID-19 vaccine, with the exception of low magnitude higher red cell distribution width (consistent with a regenerative erythroid response) and lower A:G ratios (resulting from acute phase response) in animals administered Pfizer-BioNTech COVID-19 vaccine. Macroscopic pathology and organ weight changes were also consistent with immune activation and inflammatory response and included increased size and weight of draining iliac lymph nodes and spleen. Vaccine-related microscopic findings at the end of the dosing phase consisted of edema and inflammation in injection sites and surrounding tissues, increased cellularity in the draining iliac lymph nodes, bone marrow and spleen and hepatocyte vacuolation in the liver. Vacuolation of hepatocytes, the only liver microscopic finding, was not associated with any microscopic evidence of hepatic injury or hepatic functional effects (ie, liver functional enzymes were not elevated) and is believed to be associated with hepatocyte uptake of the LNP lipids.[5] Microscopic findings at the end of the dosing phase were partially or completely recovered in all animals at the end of the 3-week recovery period for Pfizer-BioNTech COVID-19 vaccine. A robust immune response was elicited to the Pfizer-BioNTech COVID-19 vaccine antigen.

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In summary, the nonclinical safety findings related to Pfizer-BioNTech COVID-19 vaccine administration primarily represent an expected immune reaction to vaccine administration and are clinically manageable or acceptable risks in the intended population. The key safety findings regarding Pfizer-BioNTech COVID-19 vaccine from nonclinical studies and their relevance to human usage are presented in Table 2. There was no evidence of vaccine-elicited disease enhancement.

Table 2. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Nonclinical Studies [a,b]	Relevance to Human Usage
Pharmacology	
NHP Challenge Model • No evidence of vaccine-elicited disease enhancement	• Suggests low risk of vaccine-enhanced disease in humans; being investigated in CTs.
Toxicity	
Injection site reactions: • Injection site reactions were common and reversible or showed signs of reversibility at the end of the 3-week recovery period in nonclinical studies.	• In common with other vaccines, Pfizer-BioNTech COVID-19 vaccine administration has the potential to generate injection site reactions such as edema and erythema at the injection sites.
Inflammation and immune activation: • Evidence of inflammation or immune activation was common, reversible, and included transiently higher body temperature, higher circulating WBCs, and higher acute phase reactants. Secondarily, transiently lower body weights, reticulocytes, platelets, and RBC mass parameters were observed.	• In common with all vaccines, Pfizer-BioNTech COVID-19 vaccine administration has the potential to generate inflammation which can lead to increased body temperature, higher circulating WBCs and higher acute phase proteins. • Decreased reticulocytes have not been observed in humans treated with the LNP-siRNA pharmaceutical Onpattro[4], suggesting this finding in rats is a species-specific effect. • Pfizer-BioNTech COVID-19 vaccine administration has the potential to transiently decrease platelets and RBC mass parameters. These slight decreases are not likely to be clinically meaningful due to their small magnitude.

a. Safety pharmacology, genotoxicity, and carcinogenicity studies were not conducted, in accordance with 2005 WHO vaccine guideline, as they are generally not considered necessary to support development and licensure of vaccines for infectious diseases.[3] In addition, the components of the vaccine construct are lipids and RNA and are not expected to have carcinogenic or genotoxic potential.
b. A DART study evaluating Pfizer-BioNTech COVID-19 vaccine will be completed in Q1 2021.

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2.1.2. Clinical

2.1.2.a. Limitations of the Human Safety Database

The pivotal study was initially planned to enroll approximately 30,000 participants, which would have a probability of 78% of detecting an AE with a frequency of 0.01% (1/1000) and a probability of 95% of detecting an AE with a frequency of 0.02% (1/500). The protocol was amended to enroll 44,000 participants, which would slightly enhance the ability to detect AEs. However, rarer events might not be detected.

Participants are planned to be followed for up to 24 months. This is particularly relevant for assessing the potential for late-occurring adverse reactions, such as the theoretical risk of VAED.

2.1.2.a.1. Clinical Trial Exposure

Brief Overview of Development

Pfizer-BioNTech COVID-19 vaccine has been developed for the prevention of COVID-19 caused by the virus SARS-CoV-2 for use in participants ≥16 years of age.

BioNTech is conducting a German first-in-human dose level–finding Phase 1/2 study (BNT162-01) to gather safety and immunogenicity data to enable evaluation of 4 vaccines candidates individually to inform the overall clinical development of a COVID-19 vaccine.

BNT162-01 is not conducted under the US IND application but is being conducted under a German Clinical Trial Application. The protocol for this study is provided in Module 5 (Module 5.3.5.1 Clinical Study Protocol BNT162-01) of IND 019736. Please refer to Module 1.4.4 for location details.

Four vaccine candidates were evaluated in Study BNT162-01. Based on safety and immunogenicity results from this study, 2 vaccine candidates, BNT162b1 and BNT162b2, were selected for evaluation in Study C4591001, which is a Phase 1/2/3 randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate-selection, and efficacy study in healthy adults (conducted under IND 019736 – Please refer to Module 1.4.4 for Study C4591001 location details).

Phase 1 of Study C4591001 comprised dose-level–finding evaluations of the 2 selected vaccine candidates; multiple dose levels (some corresponding to those evaluated in Study BNT162-01) were evaluated. Study vaccine was administered using the same 2-dose schedule as in Study BNT162-01 (21 days apart). Dose levels were administered first to an 18- to 55-year age cohort, then to a 65- to 85-year age cohort.

Both vaccine candidate constructs were safe and well tolerated. BNT162b2 at the 30-µg dose level was selected and advanced to the Phase 2/3 expanded cohort and efficacy evaluation primarily because:

- the reactogenicity profile for BNT162b2 was more favorable than BNT162b1 in both younger and older adults with similar immunogenicity results;

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- in the NHP challenge study (VR-VTR-10671 – Cross ref. with Section 2.1.1), a trend toward earlier clearance of BNT162b2 was observed in the nose.

Phase 2 of the study (for which enrollment has completed) comprised the evaluation of safety and immunogenicity data for the first 360 participants (180 from the active vaccine group and 180 from the placebo group, with each group divided between the younger and older age cohorts) entering the study after completion of Phase 1.

The Phase 3 part of the study (which is ongoing) evaluates the efficacy and safety in all participants (including the first 360 participants from Phase 2). Phase 3 introduced enrollment of adolescents 16 to 17 years of age to be evaluated with the 18- to 55-year-old cohort, as well as enrollment of a 12- to ≤16-year-old cohort, and immunogenicity data from adolescents 12 to ≤16 years of age (Table 5 - adolescents 12 to ≤16 years) are anticipated to bridge to the 16- to 25-year-old cohort.

The efficacy evaluation is event-driven, with prespecified interim analyses after accrual of at least 62, 92, and 120 cases and a final analysis at 164 cases.

Clinical Trial Exposure

Clinical study exposure data are being provided for ongoing studies as of 14 November 2020 for study C4591001 and as of 02 October 2020 for study BNT162-01.

At the DLP, a total of 43,734 participants were vaccinated in the Pfizer-BioNTech COVID-19 vaccine clinical development program:

- 21,937 participants were exposed to BNT162b2 (Pfizer-BioNTech COVID-19 vaccine), including 96 participants from study BNT162-01.

- 21,797 participants were exposed to PLACEBO (none from study BNT162-01).

Population for analysis of CTs data in this US Pharmacovigilance Plan includes the following 2 studies:

- C4591001: Phase 1/2/3, placebo-controlled, observer-blind, dose-finding, study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals.

- BNT162-01: A multi-site, phase I/II, 2-part, dose-escalation trial investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines against COVID-19 using different dosing regimens in healthy adults.

- Exposure to Pfizer-BioNTech COVID-19 vaccine for participants in 2 ongoing studies by number of doses, and demographic characteristics is shown in Table 8 through Table 13.

- In addition, exposure in clinical studies in special populations is provided in Table 15.

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Table 3. Exposure to BNT162b2 by Age Group and Dose (C4591001)

Age Group Dose Exposure (Number of Doses Received)	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
≥16 years to ≤17 years		
Vaccine 30 µg		
1 Dose	61	61
2 Doses	77	154
Total	138	215
≥18 years to ≤55 years		
Vaccine 10 µg		
2 Doses	12	24
Total	12	24
Vaccine 20 µg		
2 Doses	12	24
Total	12	24
Vaccine 30 µg		
1 Dose	825	825
2 Doses	11830	23660
Total	12655	24485
>55 years		
Vaccine 10 µg		
2 Doses	12	24
Total	12	24
Vaccine 20 µg		
2 Doses	12	24
Total	12	24

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Table 3. Exposure to BNT162b2 by Age Group and Dose (C4591001)

Age Group Dose Exposure (Number of Doses Received)	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Vaccine 30 µg		
1 Dose	323	323
2 Doses	8629	17258
Total	8952	17581

Note: 30 µg includes data from phase 1 and phase 2/3.
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Table 4. Exposure to BNT162b2 by Age Group and Dose (BNT162-01)

Age Group Dose Exposure (Number of Doses Received)	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
≥18 years to ≤55 years		
Vaccine 1 µg		
1 Dose	1	1
2 Doses	11	22
Total	12	23
Vaccine 3 µg		
1 Dose	0	0
2 Doses	12	24
Total	12	24
Vaccine 10 µg		
1 Dose	1	1
2 Doses	11	22
Total	12	23
Vaccine 20 µg		
1 Dose	0	0
2 Doses	12	24
Total	12	24

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Table 4. Exposure to BNT162b2 by Age Group and Dose (BNT162-01)

Age Group Dose Exposure (Number of Doses Received)	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
Vaccine 30 µg		
1 Dose	0	0
2 Doses	12	24
Total	12	24
>55 years		
Vaccine 1 µg		
1 Dose	0	0
2 Doses	0	0
Total	0	0
Vaccine 3 µg		
1 Dose	0	0
2 Doses	0	0
Total	0	0
Vaccine 10 µg		
1 Dose	0	0
2 Doses	12	24
Total	12	24

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Table 4. Exposure to BNT162b2 by Age Group and Dose (BNT162-01)

Age Group Dose Exposure (Number of Doses Received)	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
Vaccine 20 µg		
1 Dose	0	0
2 Doses	12	24
Total	12	24
Vaccine 30 µg		
1 Dose	0	0
2 Doses	12	24
Total	12	24

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Table 5. Exposure to BNT162b2 by Age Group and Dose – Children and Elderly Subjects (C4591001)

Age Group Dose Exposure (Number of Doses Received)	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
≥12 years to ≤15 years		
Vaccine 30 µg		
1 Dose	1	1
2 Doses	48	96
Total	49	97
≥65 years		
Vaccine 10 µg		
2 Doses	12	24
Total	12	24
Vaccine 20 µg		
2 Doses	12	24
Total	12	24
Vaccine 30 µg		
1 Dose	121	121
2 Doses	4435	8870
Total	4556	8991

Note: 30 µg includes data from phase 1 and phase 2/3.
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Table 6. Exposure to BNT162b2 by Dose (Totals) (C4591001)

Dose Exposure (Number of Doses Received)	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Vaccine 10 µg		
2 Doses	24	48
Total	24	48
Vaccine 20 µg		
2 Doses	24	48
Total	24	48
Vaccine 30 µg		
1 Dose	1209	1209
2 Doses	20536	41072
Total	21745	42281

Note: 30 µg includes data from phase 1 and phase 2/3.
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Table 7. Exposure to BNT162b2 by Dose (Totals) (BNT162-01)

Dose Exposure (Number of Doses Received)	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
Vaccine 1 µg		
1 Dose	1	1
2 Doses	11	22
Total	12	23
Vaccine 3 µg		
1 Dose	0	0
2 Doses	12	24
Total	12	24
Vaccine 10 µg		
1 Dose	1	1
2 Doses	23	46
Total	24	47
Vaccine 20 µg		
1 Dose	0	0
2 Doses	24	48
Total	24	48

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Table 7. Exposure to BNT162b2 by Dose (Totals) (BNT162-01)

Dose Exposure (Number of Doses Received)	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
Vaccine 30 µg		
1 Dose	0	0
2 Doses	24	48
Total	24	48

PFIZER CONFIDENTIAL SDTM Creation: 03NOV2020 (21:23) Source Data: adsl Table Generation: 17NOV2020 (13:08) (Cutoff date:02OCT2020, Snapshot Date: 02OCT2020)
Output File: ex_b2_dose.rtf

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Table 8. Exposure to BNT162b2 by Dose, Age Group, and Gender (C4591001)

Dose / Age Group	Number of Subjects Exposed to BNT162b2		Total Number of Vaccine Doses	
	Male	Female	Male	Female
Vaccine 10 µg				
≥18 years to ≤55 years	5	7	10	14
>55 years	2	10	4	20
Total	7	17	14	34
Vaccine 20 µg				
≥18 years to ≤55 years	6	6	12	12
>55 years	5	7	10	14
Total	11	13	22	26
Vaccine 30 µg				
≥16 years to ≤17 years	75	63	117	98
≥18 years to ≤55 years	6437	6218	12397	12088
>55 years	4680	4272	9177	8404
Total	11192	10553	21691	20590

Note: 30 µg includes data from phase 1 and phase 2/3.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:49) Source Data: adsl Table Generation: 19NOV2020 (00:22) (Cutoff date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: (CDISC)/C4591001_RMP_Phase1_2_3/adsl_s932

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Table 9. Exposure to BNT162b2 by Dose, Age Group, and Gender (BNT162-01)

Dose Age Group	No. of Subjects Exposed to BNT162b2		Total No. of Vaccine Doses	
	Male	Female	Male	Female
Vaccine 1 µg				
≥18 years to ≤55 years	7	5	14	9
>55 years	0	0	0	0
Total	7	5	14	9
Vaccine 3 µg				
≥18 years to ≤55 years	5	7	10	14
>55 years	0	0	0	0
Total	5	7	10	14
Vaccine 10 µg				
≥18 years to ≤55 years	4	8	8	15
>55 years	8	4	16	8
Total	12	12	24	23
Vaccine 20 µg				
≥18 years to ≤55 years	2	10	4	20
>55 years	6	6	12	12
Total	8	16	16	32

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Table 9. Exposure to BNT162b2 by Dose, Age Group, and Gender (BNT162-01)

Dose Age Group	No. of Subjects Exposed to BNT162b2		Total No. of Vaccine Doses	
	Male	Female	Male	Female
Vaccine 30 µg				
≥18 years to ≤55 years	8	4	16	8
>55 years	4	8	8	16
Total	12	12	24	24

PFIZER CONFIDENTIAL SDTM Creation: 03NOV2020 (21:23) Source Data: adsl Table Generation: 18NOV2020 (15:12) (Cutoff date:02OCT2020, Snapshot Date: 02OCT2020)
Output File: ex_b2_age_dose_sex2.rtf

FDA-CBER-2021-5683-1789298

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Table 10. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001)

Age Group Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Subjects ≥16 years to ≤17 years		
Vaccine 30 µg		
Racial Origin		
White	102	158
Black or African American	21	35
Asian	7	8
Native Hawaiian or other Pacific Islander	2	4
Multiracial	6	10
Total	138	215
Ethnic Origin		
Hispanic/Latino	17	24
Non-Hispanic/non-Latino	121	191
Total	138	215
Subjects ≥18 years to ≤55 years		
Vaccine 10 µg		
Racial Origin		
White	11	22
Asian	1	2
Total	12	24
Ethnic Origin		
Hispanic/Latino	1	2
Non-Hispanic/non-Latino	11	22
Total	12	24
Vaccine 20 µg		

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Table 10. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001)

Age Group Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Racial Origin		
White	10	20
Black or African American	2	4
Total	12	24
Ethnic Origin		
Hispanic/Latino	1	2
Non-Hispanic/non-Latino	11	22
Total	12	24
Vaccine 30 µg		
Racial Origin		
White	9917	19153
Black or African American	1400	2725
Asian	681	1332
American Indian or Alaska Native	118	211
Native Hawaiian or other Pacific Islander	40	79
Multiracial	418	825
Not reported	81	160
Total	12655	24485
Ethnic Origin		
Hispanic/Latino	4001	7807
Non-Hispanic/non-Latino	8590	16557
Not reported	64	121
Total	12655	24485
Subjects >55 years		

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Table 10. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001)

Age Group Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Vaccine 10 µg		
Racial Origin		
White	12	24
Total	12	24
Ethnic Origin		
Non-Hispanic/non-Latino	12	24
Total	12	24
Vaccine 20 µg		
Racial Origin		
White	12	24
Total	12	24
Ethnic Origin		
Non-Hispanic/non-Latino	12	24
Total	12	24
Vaccine 30 µg		
Racial Origin		
White	7842	15403
Black or African American	671	1312
Asian	248	490
American Indian or Alaska Native	42	80
Native Hawaiian or other Pacific Islander	15	29
Multiracial	112	223
Not reported	22	44
Total	8952	17581

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Table 10. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (C4591001)

Age Group Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Ethnic Origin		
Hispanic/Latino	1655	3254
Non-Hispanic/non-Latino	7241	14215
Not reported	56	112
Total	8952	17581

Note: 30 µg includes data from phase 1 and phase 2/3.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:49) Source Data: adsl Table Generation: 19NOV2020 (00:22) (Cutoff date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: (CDISC)/C4591001 RMP Phase1 2 3/adsl s942

Table 11. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)

Age Group Dose Race/Ethnic Origin	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
Subjects ≥18 to ≤55 years		
Vaccine 1 µg		
Racial Origin		
White	12	23
Black or African American	0	0
Asian	0	0

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Table 11. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)

Age Group Dose Race/Ethnic Origin	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	12	23
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	12	23
Not reported	0	0
Unknown	0	0
Total	12	23

FDA-CBER-2021-5683-1789303

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Table 11. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)

Age Group Dose Race/Ethnic Origin	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
Subjects ≥18 to ≤55 years		
Vaccine 3 µg		
Racial Origin		
White	12	24
Black or African American	0	0
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	12	24
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	12	24
Not reported	0	0
Unknown	0	0
Total	12	24

FDA-CBER-2021-5683-1789304

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Table 11. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)

Age Group Dose Race/Ethnic Origin	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
Subjects ≥18 to ≤55 years		
Vaccine 10 µg		
Racial Origin		
White	12	23
Black or African American	0	0
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	12	23
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	12	23
Not reported	0	0
Unknown	0	0
Total	12	23

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Table 11. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)

Age Group Dose Race/Ethnic Origin	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
Subjects ≥18 to ≤55 years		
Vaccine 20 µg		
Racial Origin		
White	12	24
Black or African American	0	0
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	12	24
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	12	24
Not reported	0	0
Unknown	0	0
Total	12	24

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Table 11. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)

Age Group Dose Race/Ethnic Origin	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
Subjects ≥18 to ≤55 years		
Vaccine 30 µg		
Racial Origin		
White	12	24
Black or African American	0	0
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	12	24
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	12	24
Not reported	0	0
Unknown	0	0
Total	12	24

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Table 11. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)

Age Group Dose Race/Ethnic Origin	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
Subjects >55 to ≤85 years		
Vaccine 1 µg		
Racial Origin		
White	0	0
Black or African American	0	0
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	0	0
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	0	0
Not reported	0	0
Unknown	0	0
Total	0	0

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Table 11. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)

Age Group Dose Race/Ethnic Origin	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
Subjects >55 to ≤85 years		
Vaccine 3 µg		
Racial Origin		
White	0	0
Black or African American	0	0
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	0	0
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	0	0
Not reported	0	0
Unknown	0	0
Total	0	0

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Table 11. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)

Age Group Dose Race/Ethnic Origin	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
Subjects >55 to ≤85 years		
Vaccine 10 µg		
Racial Origin		
White	12	24
Black or African American	0	0
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	12	24
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	12	24
Not reported	0	0
Unknown	0	0
Total	12	24

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Table 11. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)

Age Group Dose Race/Ethnic Origin	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
Subjects >55 to ≤85 years		
Vaccine 20 µg		
Racial Origin		
White	12	24
Black or African American	0	0
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	12	24
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	12	24
Not reported	0	0
Unknown	0	0
Total	12	24

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Table 11. Exposure to BNT162b2 by Age Group, Dose, and Race/Ethnic Origin (BNT162-01)

Age Group Dose Race/Ethnic Origin	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
Subjects >55 to ≤85 years		
Vaccine 30 µg		
Racial Origin		
White	12	24
Black or African American	0	0
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	12	24
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	12	24
Not reported	0	0
Unknown	0	0
Total	12	24

PFIZER CONFIDENTIAL SDTM Creation: 03NOV2020 (21:23) Source Data: adsl Table Generation: 17NOV2020 (12:53) (Cutoff date:02OCT2020, Snapshot Date: 02OCT2020)
Output File: ex_b2_age_dose_race.rtf

FDA-CBER-2021-5683-1789312

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Table 12. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (C4591001)

Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Vaccine 10 µg		
Racial Origin		
White	23	46
Asian	1	2
Total	24	48
Ethnic Origin		
Hispanic/Latino	1	2
Non-Hispanic/non-Latino	23	46
Total	24	48
Vaccine 20 µg		
Racial Origin		
White	22	44
Black or African American	2	4
Total	24	48
Ethnic Origin		
Hispanic/Latino	1	2
Non-Hispanic/non-Latino	23	46
Total	24	48
Vaccine 30 µg		
Racial Origin		
White	17861	34714
Black or African American	2092	4072
Asian	936	1830
American Indian or Alaska Native	160	291

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Table 12. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (C4591001)

Dose Race/Ethnic Origin	Number of Subjects Exposed to BNT162b2	Total Number of Vaccine Doses
Native Hawaiian or other Pacific Islander	57	112
Multiracial	536	1058
Not reported	103	204
Total	21745	42281
Ethnic Origin		
Hispanic/Latino	5673	11085
Non-Hispanic/non-Latino	15952	30963
Not reported	120	233
Total	21745	42281

Note: 30 µg includes data from phase 1 and phase 2/3.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:49) Source Data: adsl Table Generation: 19NOV2020 (00:23) (Cutoff date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: (CDISC)/C4591001_RMP_Phase1_2_3/adsl_s952

FDA-CBER-2021-5683-1789314

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Table 13. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (BNT162-01)

Dose Race/Ethnic Origin	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
Vaccine 1 µg		
Racial Origin		
White	12	23
Black or African American	0	0
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	12	23
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	12	23
Not reported	0	0
Unknown	0	0
Total	12	23

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Table 13. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (BNT162-01)

Dose Race/Ethnic Origin	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
Vaccine 3 µg		
Racial Origin		
White	12	24
Black or African American	0	0
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	12	24
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	12	24
Not reported	0	0
Unknown	0	0
Total	12	24

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Table 13. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (BNT162-01)

Dose Race/Ethnic Origin	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
Vaccine 10 µg		
Racial Origin		
White	24	47
Black or African American	0	0
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	24	47
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	24	47
Not reported	0	0
Unknown	0	0
Total	24	47

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Table 13. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (BNT162-01)

Dose Race/Ethnic Origin	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
Vaccine 20 µg		
Racial Origin		
White	24	48
Black or African American	0	0
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	24	48
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	24	48
Not reported	0	0
Unknown	0	0
Total	24	48

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Table 13. Exposure to BNT162b2 by Dose and Race/Ethnic Origin (BNT162-01)

Dose Race/Ethnic Origin	No. of Subjects Exposed to BNT162b2	Total No. of Vaccine Doses
Vaccine 30 µg		
Racial Origin		
White	24	48
Black or African American	0	0
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not Reported	0	0
Unknown	0	0
Total	24	48
Ethnic Origin		
Hispanic/Latino	0	0
Non-Hispanic/non-Latino	24	48
Not reported	0	0
Unknown	0	0
Total	24	48

PFIZER CONFIDENTIAL SDTM Creation: 03NOV2020 (21:23) Source Data: adsl Table Generation: 17NOV2020 (13:09) (Cutoff date:02OCT2020, Snapshot Date: 02OCT2020)
Output File: ex_b2_dose_race.rtf

FDA-CBER-2021-5683-1789319

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Table 14. Exposure to BNT162b2 (30 µg) by Special Population (C4591001)

Population	Number of Subjects Exposed to BNT162b2 (30 µg) (N[a]= 21720) n[b]	Total Number of Vaccine Doses
Subjects with any baseline comorbidity	10017	25215
AIDS/HIV	99	177
Any Malignancy + Metastatic Solid Tumor + Leukemia + Lymphoma	845	1660
Chronic Pulmonary Disease	1730	3379
Renal Disease	139	274
Rheumatic Disease	75	142
Mild Liver Disease + Moderate or Severe Liver Disease	145	282
Cerebrovascular Disease + Peripheral Vascular Disease + Myocardial Infarction + Congestive Heart Failure	645	1265
Dementia	7	14
Diabetes With/Without Chronic Complication	1693	3301
Hemiplegia or Paraplegia	4	8
Peptic Ulcer Disease	62	120
Obese (≥30.0 kg/m^2)	7488	14593

Note: Comorbidity is based Charlson Comorbidity Index categories. Participants identified as belonging to these categories were identified by medical history data collected during the study.
Note: 30 µg includes data from phase 1 and phase 2/3.
Note: Hemiplegia or Paraplegia only includes preferred terms Hemiplegia and Paraplegia.
a. n = Number of subjects reporting at least 1 occurrence of any comorbidity or BMI (≥30.0 kg/m ^{2}).
b. N = number of subjects in the specified group.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:04) Source Data: admh Table Generation: 18NOV2020 (23:16) (Cutoff date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: (CDISC)/C4591001 RMP Phase1 2 3/admh s953

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2.1.2.a.2. Inclusion and Exclusion Criteria

Detailed descriptions of all inclusion and exclusion criteria for clinical studies are provided in the individual CSRs which were filed to IND 019736. Please refer to Module 1.4.4 for details (Module 5.3.5.1, Section 9.3.1 and Section 9.3.2).

Inclusion criteria

- Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

- Healthy participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. In order for the overall Phase 3 study population to be as representative and diverse as possible, the inclusion of participants with known chronic stable infection with HIV, HCV, or HBV was permitted as the study progressed. Specific criteria for these Phase 3 participants can be found in the C4591001 protocol, Section 10.8 (Please refer to Module 1.4.4 for location details).

- Phase 2/3 only: Participants who, in the judgment of the investigator, are at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, front-line essential workers, and others).

Exclusion criteria

The participants enrolled were 12 years of age and older; with the 12- to ≤16-year-old cohort most recently being included in the protocol. Phase 1 exclusion criteria were stricter than criteria in Phases 2 and 3 of the study. Participants were excluded from the studies according to the general criteria listed below:

- **Previous vaccination with any coronavirus vaccine**

  Reason for exclusion: To avoid confouding the assessment of serological or clinical immune response in the study population.

  Is it considered to be included as missing information? No.

  Rationale: Minimal potential clinical impact on the target population.

- **Previous clinical or microbiological diagnosis of COVID-19**

  Reason for exclusion: Phase 1 excluded participants with a previous clinical or microbiological diagnosis of COVID-19 because these participants may have some degree of protection from subsequent infection by SARS-CoV-2 and therefore would confound the pivotal efficacy endpoint. During Phase 2/3, participants with prior undiagnosed infection were allowed to be enrolled. Screening for SAR-CoV-2 with nucleic acid amplification test by nasal swab or antibodies to non-vaccine SARS-CoV-2

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antigen by serology was not conducted before vaccine administration in Phase 2/3, but samples were taken to run these assays after vaccination, thus identifying participants with unidentified prior infection. This group will be assessed to identify whether prior infection affects safety.

Is it considered to be included as missing information? No.

Rationale: Safety in study participants with prior infection will be assessed in the pivotal study.

- **Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.**

  Reason for exclusion: Immunocompromised participants may have impaired immune responses to vaccines and would therefore limit the ability to demonstrate efficacy, which is the primary pivotal endpoint.

  Is it considered to be included as missing information? No.

  Rationale: Participants with potential immunodeficient status were not specifically included in the study population. However, since the study population is intended to be as representative as possible of the vulnerable population to COVID-19 illness, sub-analyses of immunogenicity data in future studies may provide further understanding of immune responses in this population.

- **Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study**

  Reason for exclusion: To avoid confounding the assessment of serological or clinical immune response in the study population.

  Is it considered to be included as missing information? No.

  Rationale: No impact on the safety of the target population.

- **Women who are pregnant or breastfeeding**

  Reason for exclusion: To avoid use in a vulnerable population.

  Is it considered to be included as missing information? Yes.

  Rationale: It is not known if maternal vaccination with Pfizer-BioNTech COVID-19 vaccine would have unexpected negative consequences to the embryo or fetus.

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- **Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study**

  Reason for exclusion: To avoid misleading results deriving from non-compliance to study procedures.

  Is it considered to be included as missing information? No.

  Rationale: Safety profile of Pfizer-BioNTech COVID-19 vaccine is not expected to differ in these subjects when properly administered.

2.1.2.a.2.1. Non-Study Post-Authorization Exposure

Not applicable. At the DLP, Pfizer-BioNTech COVID-19 vaccine had not been marketed in any country/region.

Method Used to Calculate Exposure

Not applicable.

Exposure

Not applicable.

2.1.2.a.3. Regulatory Actions Related to Safety

Not applicable.

2.1.2.b. Populations Not Studied in the Pre-Approval Phase

There has been limited exposure to Pfizer-BioNTech COVID-19 vaccine in some special populations and no epidemiologic studies have been conducted in pregnant/lactating women, pediatric participants (<16 years of age), and specific subpopulations that were excluded from the Pfizer-BioNTech COVID-19 vaccine program.

Table 15. Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of special population	Exposure
Pregnant women	Available data on Pfizer-BioNTech COVID-19 vaccine administered to pregnant women are insufficient to inform on vaccine-associated risks in pregnancy. Therefore, Pfizer-BioNTech COVID-19 vaccine is not recommended for use during pregnancy. Through the DLP, there were 11 cases (11 events) originating from Study C4591001, and all were unique pregnancies.

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Table 15. Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of special population	Exposure
Breastfeeding women	Breastfeeding women were not included in the Pfizer-BioNTech COVID-19 vaccine clinical development program. Data are not available to assess the effects of Pfizer-BioNTech COVID-19 vaccine on the breastfed infant or on milk production/excretion. Therefore, Pfizer-BioNTech COVID-19 vaccine is not recommended during breastfeeding. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Pfizer-BioNTech COVID-19 vaccine and any potential adverse effects on the breastfed newborn infant/toddler from Pfizer-BioNTech COVID-19 vaccine or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptible to disease prevented by the vaccine. There were no CT cases indicative of exposure during breastfeeding. Women who were breastfeeding were excluded from study participation.
Participants with relevant comorbidities: • Participants with hepatic impairment • Participants with renal impairment • Participants with cardiovascular disease • Immunocompromised participants • Participants with a disease severity different from inclusion criteria in CTs	Healthy participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, were included. This allowed enrollment of a proportion of participants with common comorbidities such as cardiovascular diseases including hypertension, chronic pulmonary diseases, asthma, chronic liver disease, BMI >30 kg/m^2, participants with stage 3 or worse chronic kidney disease, and participants with varying disease severity. Please refer to Table 14 for the exposure of special populations. Participants with potential immunodeficient status were not specifically included in the study population.
Participants of different racial and/or ethnic origin	Please refer to Table 10 to Table 13 for exposure information by ethnic origin from the studies.
Subpopulations carrying known and relevant polymorphisms	No data available.
Pediatric participants	The safety and effectiveness in individuals younger than 16 years of age have not yet been established. Forty-nine (49) children 12 to 15 years of age received Pfizer-BioNTech COVID-19 vaccine (Table 5).
Elderly (≥65 years old)	Clinical studies of Pfizer-BioNTech COVID-19 vaccine included 4580 participants 65 years of age and over. Please refer to 2.1.2.a.1 *Clinical Trial Exposure* and Table 5.

Abbreviations: BMI = body mass index; CT = clinical trial; DLP = data lock point;
PVP = pharmacovigilance plan

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2.1.2.c. Adverse Events / Adverse Reactions

2.1.2.c.1. Identification of Safety Concern in the Initial PVP Submission

Risks not Considered Important for Inclusion in the List of Safety Concerns in the PVP

Not all potential or identified risks for the vaccine are considered to meet the level of importance necesitating inclusion in the list of safety concerns in the PVP:

- Risks with minimal and temporary clinical impact on patients (in relation to the severity of the disease prevented) are not included in the list of safety concerns. For example, the determined adverse reactions: Injection site pain, Fever, Chills, Fatigue, Headache, Muscle pain, Joint pain and Lymphadenopathy (enlarged lymph nodes).

- Very rare potential risks of vaccines that are known to healthcare professionals are not included in the list of safety concerns. For example, anaphylactic reactions. Although the potential clinical consequences of an anaphylactic reaction are severe, this is a known risk of vaccines to healthcare professionals and patients, occurs with a very rare frequency, and is an acceptable potential risk in relation to the severity of the disease prevented.

2.1.2.c.2. Important Identified and Potential Risks and Missing Information

Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risks

None.

Important Potential Risks

Table 16. Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Potential mechanisms, evidence source and strength of evidence	This potential risk is theoretical because it has not been described in association with the Pfizer-BioNTech COVID-19 vaccine or it has not been reported from any other late phase clinical trial of other human vaccine. Animal models of SARS-CoV-2 infection have not shown evidence of VAED after immunization, whereas cellular immunopathology has been demonstrated after viral challenge in some animal models administered SARS-CoV-1 (murine, ferret and non-human primate models) or MERS-CoV (mice model) vaccines.[1,6] This potential risk has been included based on these animal data with these related betacoronaviruses. Historically, disease enhancement in vaccinated children following infection with natural virus has been observed with an inactivated respiratory syncytial virus vaccine. [7] Potential mechanisms of enhanced disease may include both T cell-mediated [an immunopathological response favoring T helper cell type 2 (T_H2) over T helper cell type 1 (T_H1)] and antibody-mediated activity (antibody responses with insufficient neutralizing activity leading to formation of immune complexes and activation of complement or allowing for Fc-mediated increase in viral entry to cells).[8]

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Table 16. Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Characterization of the risk

Confirmed Case of Postvaccination Severe COVID-19 – Safety Population (C4591001)

Timing	BNT162b2 (30 µg) (N[a]=21721) n[b] (%)	BNT162b2 (30 µg) (N[a]=21721) (95% CI[c])	Placebo (N[a]=21729) n[b] (%)	Placebo (N[a]=21729) (95% CI[c])
PD1 Before Dose 2	0	(0.0, 0.0)	4 (0.0)	(0.0, 0.0)
Within 7 days PD1	0	(0.0, 0.0)	0	(0.0, 0.0)
Within 14 days PD1	0	(0.0, 0.0)	3 (0.0)	(0.0, 0.0)
PD2	1 (0.0)	(0.0, 0.0)	5 (0.0)	(0.0, 0.1)
Within 7 days PD2	0	(0.0, 0.0)	1 (0.0)	(0.0, 0.0)
Within 14 days PD2	0	(0.0, 0.0)	2 (0.0)	(0.0, 0.0)
Total[d]	1 (0.0)	(0.0, 0.0)	9 (0.0)	(0.0, 0.1)

Note: This table includes subjects from Phase 2/3 only.
Abbreviations: PD1 = post-dose 1; PD2 = post-dose 2.
a. N = number of subjects in the specified group. This value is the denominator for the percentage calculations.
b. n = Number of subjects reporting at least 1 occurrence of the specified event.
c. Exact 2-sided CI based on the Clopper and Pearson method.
d. Total is the sum of PD1 and PD2.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:49) Source Data: adc19ef Table Generation: 19NOV2020 (00:22) (Cutoff date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: (CDISC)/C4591001_RMP_Phase1_2_3/adeff_s901

If VAED/VAERD were to occur in vaccinated individuals, it may manifest as a modified and/or more severe clinical presentation of SARS-CoV-2 viral infection upon subsequent natural infection. This may result in individuals assumed to be at lower risk for severe COVID-19 having more severe disease, for individuals at known risk for severe COVID-19 (e.g. older or immunocompromised) having higher rates of fatal outcomes, or for observation of an unfavorable imbalance in severe COVID-19 cases in vaccinated individuals when compared to those not vaccinated. It is challenging if not impossible to assess for VAED/VAERD on an individual case basis, given the lack of specific clinical or laboratory markers at this time, rather surveillance for this theoretical risk needs to be at a population level,[9] as noted above. The table above shows a favorable balance of severe COVID-19 cases in participants receiving Pfizer-BioNTech COVID-19 vaccine versus those receiving placebo, providing reassurance against the potential risk of VAED/VAERD at this time.

Risk factors and risk groups	It is postulated that the potential risk may be increased in individuals producing lower neutralizing antibody titers or in those demonstrating waning immunity.[8,9]
Preventability	An effective vaccine against COVID-19 that produces high neutralizing titers and a T_H1 predominant $CD4^+$ T cell response and strong $CD8^+$ T cell response, is expected to mitigate the risk of VAED/VAERD;[1,8] that immune profile is elicited by BNT162b2 in clinical and preclinical studies.[10,11]
Impact on the risk-benefit balance of the biologic product	If there were an unfavorable balance in COVID-19 cases, including severe cases, in the pivotal clinical study between the vaccine and placebo groups, that may signal VAED/VAERD.
Public health impact	The potential risk of VAED/VAERD could have a public health impact if large populations of individuals are affected.

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Presentation of Missing Information

Table 17. Use in Pregnancy and Lactation

Evidence source: The safety profile of the vaccine is not known in pregnant or lactating women due to their exclusion from the pivotal clinical study. There may be pregnant women who choose to be vaccinated despite the lack of safety data. It will be important to follow these women for pregnancy and birth outcomes. The timing of vaccination in a pregnant woman and the subsequent immune response may have varying favorable or unfavorable impacts on the embryo/fetus. The clinical consequences of SARS-CoV-2 infection to the woman and fetus during pregnancy is not yet fully understood and the pregnant woman's baseline health status may affect both the clinical course of her pregnancy and the severity of COVID-19 disease. These factors and the extent to which the pregnant woman may be at risk of exposure to SARS-CoV-2 will influence the benefit risk considerations for use of the vaccine. Population in need of further characterization: The lack of data will be communicated in product labeling; clinical study of the safety and immunogenicity of Pfizer-BioNTech COVID-19 vaccine in pregnant women, is planned.

Table 18. Vaccine Effectiveness

Evidence source: Although vaccine efficacy in a controlled clinical study is the objective of the pivotal study, real-world vaccine effectiveness when Pfizer-BioNTech COVID-19 vaccine is used in a large and more diverse population is unknown. Anticipated risk/consequence of missing information: Efficacy information obtained from clinical study data will be communicated in the product labeling. Plans for post-authorization effectiveness in real-world use are being developed.

Table 19. Use in Paediatric Individuals <16 Years of Age

Evidence source: Pfizer-BioNTech COVID-19 vaccine has not been studied in paediatric individuals younger than 12 years of age due to their exclusion from the pivotal clinical study; there are limited data for paediatric individuals aged between 12 and <16 years, recently included in Phase 3 of study C4591001. Paediatric individuals may display different reactogenicity and safety profiles compared to adults, due to lower body mass and differently matured immunological responses. Population in need of further characterization: The limited data in individuals younger than 16 years of age is communicated in product labeling; a clinical study of the safety and immunogenicity of Pfizer-BioNTech COVID-19 vaccine in individuals between 12 and 15 years of age is ongoing (C4591001); 2 clinical studies of the safety, tolerability, immunogenicityand efficacy of Pfizer-BioNTech COVID-19 vaccine in individual younger than 12 years (0 to < 5 years of age and 5 to < 12 years of age) are planned.

2.1.2.d. Identified and Potential Interactions, Including Food-Biologic Product and Drug-Biologic Product Interactions

As noted in the WHO Guidelines on Nonclinical Evaluation of Vaccines,[3] pharmacokinetics testing is not required for final formulation. No interaction linked to metabolism is expected

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with vaccines. The only potential for interaction is with other vaccines administered concomitantly and with immunosuppressive drugs.

Co-administration studies with Pfizer-BioNTech COVID-19 vaccine have not been done, therefore there is not sufficient data to understand the effect on vaccine effectiveness of Pfizer-BioNTech COVID-19 vaccine or co-administered vaccines. If Pfizer-BioNTech COVID-19 vaccine is given at the same time as other injectable vaccine(s), the vaccine(s) should be administered at different injection sites.

2.1.2.e. Epidemiology of Indication and Target Population

Indication

Active immunization against COVID-19 disease caused by SARS-CoV-2 virus in individuals ≥16 years of age

Incidence:

The COVID-19 is caused by a novel coronavirus labeled as SARS-CoV-2. The disease first emerged in December 2019, when a cluster of patients with pneumonia of unknown cause was recognized in Wuhan City, Hubei Province, China.[12] The number of infected cases rapidly increased and spread beyond China throughout the world. On 30 January 2020, the WHO declared COVID-19 a Public Health Emergency of International Concern and thus a pandemic.[13]

Estimates of SARS-CoV-2 incidence change rapidly. As of 9 November 2020, the overall number of people who had been infected with SARS-CoV-2 was over 50 million worldwide. In the EU and the UK, the number of confirmed cases had accumulated to over 9 million people, corresponding to 337 per 100,000 people. Across countries in the EU, the number of confirmed cases ranged from 40 to 1,017 cases per 100,000 people. Slovakia, Greece and Hungary reported an incidence below 50 per 100,000 whereas Spain, Sweden and Luxembourg reported over 700 confirmed cases per 100,000 people.

In the US, the number of confirmed cases had reached over 10 million cases (3,126 per 100,000 people) by the beginning of November 2020. The reported numbers refer only to cases that have been tested and confirmed to be carrying the virus. There are large geographic variations in the proportion of the population tested as well as varied quality of reporting across countries. People who carry the virus but remain asymptomatic are less likely to be tested and therefore mild cases are likely underreported. The numbers should therefore be interpreted with caution.[14]

Prevalence:

The prevalence of SARS-CoV-2 infection is defined as active cases per 100,000 people including confirmed cases in people who have not recovered or died. On 9 November 2020, the overall prevalence for EU countries was 37.0 active cases per 100,000. The range of reported prevalence was 2.8 to 337.7 per 100,000 with Finland, Estonia and Hungary at the low end and Portugal, Luxembourg and Belgium at the high end.

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In the US, the prevalence on the same date was similar to the EU estimates, with 31.5 active cases per 100,000.[14]

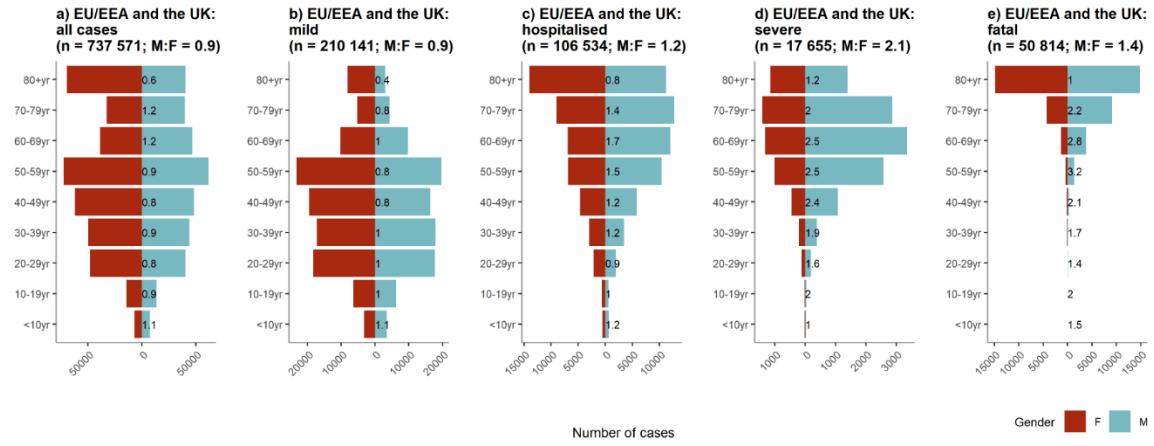
Demographics of the population in the proposed indication and risk factors for the disease:

While anyone can become infected with SARS-CoV-2, symptoms of COVID-19 disease can range from very mild (or no symptoms) to severe. Risk factors for developing severe disease, include age over 60 years, male sex, diabetes, severe obesity, chronic kidney disease and congestive heart failure.[15,16,17,18]

The ECDC has since the beginning of the pandemic continuously collected COVID-19 information from all countries who are members of EU/EEA and the UK. In their database TESSy COVID-19 case-based data, including age and gender, are available for approximately 40% of the official number of cases reported by ECDC epidemic intelligence.[19] All countries included in EU/EEA and UK, except Spain, Slovenia and Liechtenstein, have at some point during the pandemic provided case-based data to TESSy, enabling estimates of age and gender distribution representative of the European population.

According to TESSy case-based data, accessed 7 August 2020, (Figure 1), the gender distribution of persons testing positive for SARS-Cov-2 in the European population is similar for most age groups. However, males and older age groups are over-represented among the more severe cases (defined as hospitalized, severe, or fatal). Few cases were reported in people aged younger than 20 years. This data reflects the age distribution of people who met the requirements for being tested and is unlikely to reflect the actual distribution of infections in the population.[19] The distribution of age was different in the period of January-May compared to June-July. Between January and May 2020, 40% of cases were ≥60 years old and the largest proportion (18.7%) of cases were reported in the 50-59 years age group. In contrast, between June and July, persons aged ≥60 years accounted for 17.3% of cases and the largest proportion (19.5%) of cases were reported in the 20-29-year age group.[20]

Figure 1. Age-Sex distribution of COVID-19 Cases as Different Levels of Severity, EU/EEA and UK. Case-based Data from TESSy produced on 07 August 2020 [a]


a) EU/EEA and the UK: all cases (n = 737 571; M:F = 0.9)
b) EU/EEA and the UK: mild (n = 210 141; M:F = 0.9)
c) EU/EEA and the UK: hospitalised (n = 106 534; M:F = 1.2)
d) EU/EEA and the UK: severe (n = 17 655; M:F = 2.1)
e) EU/EEA and the UK: fatal (n = 50 814; M:F = 1.4)
80+yr
70-79yr
60-69yr
50-59yr
40-49yr
30-39yr
20-29yr
10-19yr
<10yr
Number of cases
Gender
F
M

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Note: "mild"= a case that has not been reported as hospitalized or a case that resulted in death.
a. Data from ECDC. COVID-19 Surveillance report. Week 31, 2020. 7 August 2020. "2.2 Age-sex pyramids".[21]

In the US, surveillance data collected between 22 January 2020 and 30 May 2020 showed a similar age distribution of infected cases in both genders (Table 20). Among 1,320,488 laboratory-confirmed COVID-19 cases, overall incidence per 100,000 persons was higher among individuals aged 40 - 49 years (541.6) and 50 - 59 years (550.5) than among those aged 60 - 69 years (478.4) and 70 - 79 years (464.2). Estimates were highest among persons aged ≥80 years (902.0) and lowest among children aged ≤9 years (51.1).[22] During June-August, the COVID-19 pandemic in the US affected a larger proportion of younger persons than during January–May 2020. In this period, incidence was highest in persons aged 20-29 years, accounting for >20% of all confirmed cases. The shift toward younger ages occurred in all four U.S. Census regions, regardless of changes in incidence during this period, and was reflected in COVID-19–like illness-related ED visits, positive SARS-CoV-2 RT-PCR test results, and confirmed COVID-19 cases.[23]

Of the 599,636 (45%) cases with information on both race and ethnicity in US surveillance data collected between 22 January 2020 and 30 May 2020, 36% were non-Hispanic white, 33% were Hispanic, 22% were black, 4% were non-Hispanic Asian, 4% were non-Hispanic, other or multiple race, 1.3% were American Indian/Alaskan Native, and <1% were non-Hispanic Native Hawaiian or other Pacific Islander.[22] An increased rate ratio of COVID-19 cases and hospitalization compared to White, non-Hispanic has been reported for all other race and ethnicity groups, underlying factors including socioeconomic status, access to health care and occupations are likely to be the actual risk factors.[24]

Table 20. Distribution and Estimated Cumulative Incidence of Reported Laboratory-Confirmed COVID-19 Cases, by Sex and Age Group — United States, 22 January – 30 May 2020[a]

	Males		Females	
Age group (years)	**Proportion (%)**	**Cumulative Incidence***	**Proportion (%)**	**Cumulative Incidence***
0-9	1.7	52.5	1.4	49.7
10-19	3.8	113.4	3.7	121.4
20-29	13.3	370.0	14.3	434.6
30-39	16.8	492.8	15.8	490.5
40-49	17.0	547.0	16.2	536.2
50-59	18.4	568.8	17.3	533.0
60-69	14.5	526.9	12.7	434.6
70-79	8.2	513.7	7.7	422.7
≥ 80	6.4	842.0	10.8	940.0

a. Data from Stokes.[22]
* Per 100,000 people

Among hospitalized cases with COVID-19 in the US, approximately 90% are over 40 years old, and between 58% to 66% are at least 60 years old.[15,25] The majority (approximately 60%) of COVID-19 patients admitted to hospitals in the US have been male.[15,17,25,26,27,28,29] African American COVID-19 patients have been reported to have an increased risk of hospitalization [15,26] and mortality, [30] compared to white patients in the United States.

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The main existing treatment options:

There are currently no other approved vaccines for active immunization against COVID-19. At the time that this vaccine was in advanced development there were other vaccines in similar late-phase development, including vaccines from Moderna (NCT04470427), Sinovac (NCT04456595), AstraZeneca (NCT04516746), and Johnson & Johnson (NCT04505722), which may subsequently be approved, as may others in earlier development.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

The natural history of COVID-19 disease is not yet fully understood. In the US, 14% of individuals testing positive for SARS-CoV-2 22 January – 30 May 2020 were reported to require hospitalization. The rate was lowest (<9%) among age groups <50 years, and highest among those older than 70 years (33%) and among patients with underlying health conditions (45.4%).[22]

Based on rates of severe disease reported in mainland China and assuming severe cases would be hospitalized, a demography-adjusted and under-ascertainment-adjusted model estimated the proportion of infected individuals requiring hospitalization. The proportions ranged from 8.2% in the age group 50-59 years to 18.4% in those older than 80 years. In the age groups below 50 years, less than 5% of infections were estimated to lead to hospitalization.[31]

Approximately 17% to 40% of those hospitalized with COVID-19 experience severe symptoms necessitating intensive care. [16,18,26] More than 75% of patients hospitalized with COVID-19 require supplemental oxygen. [16,32] The most common symptoms in hospitalized patients are fever (up to 90% of patients), dry cough (60%-86%), shortness of breath (53%-80%), fatigue (38%), nausea/vomiting or diarrhea (15%-39%), and myalgia (15%-44%).[18,25,28,32,33,34] Complications of COVID-19 include impaired function of the heart, brain, lung, liver, kidney, and coagulation system.[26,28,32] Venous and arterial thromboembolic events occur in 10% to 25% in hospitalized patients with COVID-19 and in the ICU, venous and arterial thromboembolic events may occur in up to 31% to 59% of patients.[32]

As of 28 July 2020, the total number of COVID-19 related deaths in the EU and UK was over 100,000 and, in the US more than 150,000 people had died from COVID-19.[14] Overall reported mortality among hospitalized COVID-19 patients varies from 12.8% to 26% in Europe [16,34,35] and 20%-23% in the US. [18,26,28] In the US, studies have also reported up to 40% mortality in patients admitted to the ICU.[25,26,28] Age older than 60 years, male sex, hypertension, cardiovascular disease and chronic pulmonary disease, have been shown to be independently associated with in-hospital death of COVID-19 patients.[18,25,35]

Important co-morbidities:

Important comorbidities in hospitalized COVID-19 patients include hypertension, diabetes, obesity, cardiovascular disease, chronic pulmonary disease or asthma, chronic kidney disease, cancer, and chronic liver disease.[18,22,25,27,28,29,32] Prevalence of these conditions have

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been reported to be lower in mild cases and higher among fatal cases, as shown in Table 21 below.

Table 21. Preconditions among COVID-19 Patients in EU/EEA and UK, by Severity of Disease. Case-based Data from TESSy Produced on 24 September 2020

Precondition	Mild % (N=66,257)	Hospitalized % (N=48,494)	Fatal % (N=12,796)
Asplenia	0	0	0
Asthma	1.5	3.1	4.3
Cancer, malignancy	1.3	4.1	5.4
Cardiac disorder, excluding hypertension	3.9	12.1	16.1
Chronic lung disease, excluding asthma	3.0	6.3	9.2
Current smoking	2.4	0.3	0.3
Diabetes	2.8	11.6	14.2
Haematological disorders	0.1	0.7	0.6
HIV/other immune deficiency	0.5	1.6	1.8
Hypertension	2.2	9.0	18.4
Kidney-related condition, renal disease	0.6	4.1	8.1
Liver-related condition, liver disease	0.3	1.6	1.7
Neuromuscular disorder, chronic neurological	1.3	3.8	7.2
Obesity	0.6	0.3	0.1
Other endocrine disorder, excluding diabetes	0.2	0.3	0.2
Rheumatic diseases including arthritis	0	0.1	0
Tuberculosis	0	0	0
None	***79.3***	***41.2***	***12.4***

2.1.2.f. Pharmacological Class Effects

There are no other vaccines with a mRNA platform that have been approved by competent authorities because it is a new class of vaccines. At this time there are no known safety issues in humans that are specifically related to the mRNA platform such as the one utilized in Pfizer-BioNTech COVID-19 vaccine. Theoretical concerns that have been considered have included the risk of the presence of naked extracellular RNA in the body which may lead to edema or coagulation and concerns about aberrant immune responses to the RNA or lipid particles. system. The immunogenicity and efficacy data from study C4591001 are indicative of the vaccine delivery system's success in transfecting the RNA into the appropriate target cells to stimulate an immune response. The RNA itself cannot integrate into the DNA genome.[36,37] The probability of any sequences from the vaccine RNA being integrated into the human genome by a reverse transcription mediated mechanism is considered remote, no higher than the probability of host RNA sequences being re-inserted into the genome, especially given the small quantity of RNA in the vaccine, the barriers to transfected RNA reaching the nucleus, the non-replicating nature of the vaccine RNA, the limited stability of RNA in a cellular context, and the expected targeting of transfected cells for elimination by T cells elicited by the vaccine antigen expressed from the RNA.

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3. PHARMACOVIGILANCE PLAN

Structure of the Pharmacovigilance Plan

3.1.1. Summary of Ongoing Safety Concerns

Table 22. Ongoing Safety Concerns

Important Identified Risks	None
Important Potential Risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)
Missing Information	Use in pregnancy and lactation
	Vaccine effectiveness
	Use in paediatric individuals <16 years of age

3.1.2. Routine Pharmacovigilance Practices

- Routine pharmacovigilance is a critical component of activities relating to the detection, assessment, understanding and prevention of AEs. The objective of routine pharmacovigilance is to have processes in place to assure the ongoing and timely collection, processing, follow-up, and analysis of individual AE reports globally, following global safety Standard Operating Procedures and regulatory guidance.

- Pfizer, on behalf of the MAH, monitors the safety profile of its products, evaluates issues potentially impacting product benefit-risk profiles in a timely manner, and ensures that appropriate communication of relevant information is conveyed in a timely manner to regulatory authorities and other interested parties as appropriate and in accordance with international principles and prevailing regulations.

- Pfizer, on behalf of the MAH, conducts scientific data gathering activities for the detection and evaluation of AEs in order to ensure safety monitoring, which is commensurate with product characteristics.

- Signal detection activities include periodic literature review for the life cycle of the product. This includes reviewing the medical literature for individual case reports that should be entered into the safety database as well as periodic aggregate literature review for broader signal detection.

- Safety signal evaluation requires the collection, analysis and assessment of information to evaluate whether there is a potential causal association between an event and the administration of the product and includes subsequent qualitative or quantitative characterization of the relevant safety risk to determine appropriate pharmacovigilance and risk mitigation actions.

- Routine pharmacovigilance and signal detection activities will include the use of a DCA to obtain structured follow-up information for reports of COVID-19 disease occurring in association with Pfizer-BioNTech COVID-19 vaccine use. The DCA will contain specific questions regarding the SARS-CoV-2 vaccine administered, the regimen of

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administration (number of doses and scheduling), latency between vaccination and COVID-19 disease, and course and severity of COVID-19 disease. The DCA is intended also to help characterization of the missing information vaccine effectiveness and of the important potential risk "possibility of VAED/VAERD".

- A web-based AE reporting portal will be available for vaccine providers and recipients, to assist with anticipated high volume of reports (based on expected large target population). The portal will capture key adverse event data in the initial interaction and will provide automated intake into the Pfizer safety database via E2B for safety review.

- At the country level, the Drug Safety Unit performs routine pharmacovigilance activities including the collection of AEs from various sources and the reporting of AEs to the regulatory authority as per local regulatory guidelines.

3.1.3. Action Plan for Safety Issues

Action Plan for Important Potential Risks

Table 23. Action Plan for Important Potential Risk "Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)"

Actions proposed	a. Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals (C4591001). b. Three post-authorization epidemiological safety studies, encompassing primary and secondary data collection to perform long-term active surveillance for safety events of interest, including severe or atypical COVID-19 disease, among individuals vaccinated with Pfizer-BioNTech COVID-19 vaccine.
Objective of proposed actions	a. The objective of the C4591001 study is to evaluate the safety, tolerability, immunogenicity, and efficacy of Pfizer-BioNTech COVID-19 vaccine. Further, an unfavorable imbalance between the vaccine and control groups in the frequency of COVID-19 disease, in particular for severe COVID-19 disease, may indicate the occurrence of VAED/VAERD. Surveillance is planned for 2 years following Dose 2. b. The objective of the 3 epidemiological post-authorization safety studies is to characterize the real-world incidence of safety events of interest, including events indicative of severe or atypical COVID-19 disease, among individuals vaccinated with the Pfizer-BioNTech COVID-19 vaccine under an EUA.
Rationale for proposed actions	a. C4591001: Robust and long-term monitoring throughout the clinical study for up to 2 years to assess the risk for vaccine-associated enhanced disease. b. Robust and long-term surveillance is needed to ensure comprehensive understanding of real-world safety. This surveillance strategy consists of complementary approaches to ensure timely signal identification and evaluation in populations expected to receive the vaccine under an EUA.

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Table 23. Action Plan for Important Potential Risk "Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)"

Monitoring by the sponsor for safety issue and proposed actions	a. C4591001: Protocol prespecified stopping and alert rules were set for detecting enhanced COVID-19. Participants in all stages of the study will be monitored for COVID-19 illness including severe COVID-19 from Visit 1 onward. Cases will undergo blinded review to identify whether any features of each case appear unusual, in particular greater severity. Indicators of severity may include accelerated deterioration, need for hospitalization, need for ventilation, or death. The Data Monitoring Committee, supported by an unblinded medical monitor, will look for adverse imbalances between vaccine and control groups in COVID-19 disease outcomes, in particular for cases of severe COVID-19, that may be a signal for vaccine-associated enhanced disease on an ongoing basis and at interim analyses. Stopping rules were set so that enrollment could be paused in the event of an adverse imbalance. Additional safety evaluations will include AEs of Special Interest that could represent symptoms of severe COVID-19 disease; these will be collected systemically and monitored throughout the Phase 3 study. b. 1. The collection of safety data in vaccine recipients is critical to our understanding of the vaccine safety profile and to enable efficient safety signal detection and, if needed, further risk mitigation during an EUA. In addition to the collection and monitoring of AEs reported voluntarily by healthcare professionals providing the vaccine and by individuals receiving the vaccine, active surveillance studies of the Pfizer-BioNTech COVID-19 vaccine under EUA are also planned. Please refer to the EUA Safety Surveillance Study Plan in Attachment 1 (Safety Surveillance Plan) for details on the proposed activities. 2. Long-term, active surveillance of large numbers of individuals vaccinated with the Pfizer-BioNTech COVID-19 vaccine is necessary to confirm the safety profile demonstrated in the clinical study in a broader population under real-world conditions. Availability of Pfizer-BioNTech COVID-19 vaccine through an EUA provide the earliest opportunity to initiate these studies. Pfizer-BioNTech plans to conduct active surveillance studies of individuals vaccinated with the Pfizer-BioNTech COVID-19 vaccine under EUA in populations expected to be eligible in the early stages of the EUA, eg, healthcare workers and active military, as described in Attachment 2 (C4591008 draft protocol); Attachment 3 (C4591011 draft protocol) and Attachment 4 (C4591012 draft protocol). As feasible, additional populations will be sought for inclusion as vaccine roll-out staging expands. The study period will be 30 months following availability of vaccine under EUA in target populations. The studies will capture hospitalizations, deaths and serious safety events of interest, including severe COVID-19 (which, if associated with vaccination, may indicate VAED/VAERD).

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Table 23. Action Plan for Important Potential Risk "Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)"

Milestones for evaluation and reporting	a. C4591001 (ongoing Study) • Protocol submission: 22 April 2020 (Initial version); 30 October 2020 (Amendment No. 9) • CSR submission on completion of the first efficay IA with 94 cases: 12 November 2020; • CSR submission on completion of full efficacy analysis with 164 cases: November 2020; • CSR submission upon regulatory request: at any time. • CSR submission 6 months post Dose 2: December 2021; • Final CSR submission with supplemental follow-up: August 2023. b. Three post-authorization epidemiological safety studies for EUA • Protocols draft submission: November 2020 • Interim study reports* will be generated on data collected within the following study periods post-EUA vaccination in target populations: – 31 March 2021 – 30 June 2021 – 31 December 2021 – 30 June 2022 – 31 December 2022 • Reports will be submitted within 1 month of end of interim study period. • Final study reports will be based on a study period of 30 months and submitted within 6-months of end of study. * *Note: planned report dates assume vaccine availability on 01 December 2020*

Action Plan for Missing Information

Table 24. Action Plan for Missing Information "Use in Pregnancy and Lactation"

Actions proposed	a. Clinical study to assess safety and immunogenicity in pregnant women who receive the Pfizer-BioNTech COVID-19 vaccine. b. Active surveillance epidemiological studies designed to monitor pregnancies exposed to the Pfizer-BioNTech COVID-19 vaccine under EUA within the US. As feasible, for such individuals identified, data characterizing use, timing of exposure, and adverse pregnancy outcomes will be described.
Objective of proposed actions	a. Clinical study: to assess safety and immunogenicity of Pfizer-BioNTech COVID-19 vaccine in pregnant women. b. Within the proposed real-world active surveillance studies, monitor for Pfizer-BioNTech COVID-19 vaccination during pregnancy occurring under an EUA within the US, and characterize use and outcomes as feasible.
Rationale for proposed actions	Acquisition of data in an unstudied population with potentially different safety considerations from the time vaccine is available.

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Table 24. Action Plan for Missing Information "Use in Pregnancy and Lactation"

Monitoring by the sponsor for safety issue and proposed actions	a. Monitoring via planned clinical study. b. The proposed real-world active surveillance studies are designed to monitor vaccination during pregnancy within populations expected to receive Pfizer-BioNTech COVID-19 vaccine under EUA. As feasible, this surveillance strategy may be extended to obtain more comprehensive information to characterize use and outcomes with increasing real-world vaccination during pregnancy.
Milestones for evaluation and reporting	a. Protocol submission: February 2021 Primary endpoints completion: April 2023 b. Protocols draft submission: November 2020 • Interim study reports* will be generated on data collected within the following study periods post-EUA vaccination in target populations: – 31 March 2021 – 30 June 2021 – 31 December 2021 – 30 June 2022 – 31 December 2022 • Reports will be submitted within 1 month of end of interim study period. • Final study reports will be based on a study period of 30 months and submitted within 6-months of end of study. * *Note: planned report dates assume vaccine availability on 01 December 2020*

Table 25. Action Plan for Missing Information "Vaccine Effectiveness"

Action proposed	a. Non-interventional study (test-negative design) of individuals presenting with symptoms of potential COVID-19 illness in a real-world setting. b. BNT162-01 cohort 13: Immunogenicity of Pfizer-BioNTech COVID-19 vaccine in immunocompromised subjects, including assessment of antibody responses and cell-mediated responses.
Objective of proposed actions	a. To estimate the effectiveness of the recommended regimen of Pfizer-BioNTech COVID-19 vaccine against potential COVID-19 illness requiring admission to the ED or hospital where SARS-CoV-2 is identified. b. To assess potentially protective immune responses in immunocompromised adults.
Rationale for proposed actions	a. To assess real-world effectiveness in comparison to clinical study efficacy results. b. To determine whether the Pfizer-BioNTech COVID-19 vaccine has potential to protect immunocompromised adults.
Monitoring by the sponsor for safety issue and proposed actions	a. Use of primary and secondary data sources to monitor COVID-19 infection in vaccinated individuals. b. Reactogenicity, AE and SAE assessment.

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Table 25. Action Plan for Missing Information "Vaccine Effectiveness"

Milestones for evaluation and reporting	a. Protocol submission: Q1 2021 Final CSR submission: June 2023 b. Protocol submission: November 2020 First IA submission: Q3 2021

Table 26. Action Plan for Missing Information "Use in Paediatric Individuals <16 Years of Age"

Actions proposed	a. **≥12 to ≤15 years of age**: Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals (C4591001). Randomised placebo-controlled study in 2000 subjects (1000 active vaccine) of 2 doses of BNT162b2 at a 21-day interval. b. **5 to <12 years of age**: Phase 1 open label dose-finding study to evaluate safety, tolerability, and immunogenicity and phase 2/3 placebo-controlled, observer blinded safety, tolerability, immunogenicity, and efficacy study of a SARS-CoV-2 RNA vaccine candidate against COVID-19 in healthy children and adolescents ⩾5 to <18 years of age (C4591007). Open uncontrolled escalating dose Phase 1 part, 16 subjects/dose level, up to 3 dose levels. Phase 2/3 part, randomized placebo-controlled study in 3000 subjects (1500 active vaccine) at selected dose level of BNT162b2 at a 21-day interval. Study C4591007 includes an option to study subjects 12-<18 years of age if required, with a study design matching 5- to <12-year-old. c. **0 to <5 years of age**: A phase 1 open label dose-finding study to evaluate safety, tolerability, and immunogenicity and phase 2/3 placebo-controlled, observer blinded safety, tolerability, immunogenicity, and efficacy study of a SARS-CoV-2 RNA vaccine candidate against COVID-19 in healthy toddlers, infants and children 0 to <5 years of age (Protocol number not yet assigned). Open uncontrolled escalating dose Phase 1 part, 16 subjects/dose level, up to 3 dose levels in 2 to <5 years of age, 12 to 23 months of age, 7 to < 11 months of age and 0 to 6 months of age. Randomized placebo-controlled study in 6400 subjects (3200 active vaccine) at selected dose levels of BNT162b2 at a 21-day interval in 4 strata: 2 to <5 years of age, 12 to 23 months of age, 7 to < 11 months of age and 0 to 6 months of age.

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Table 26. Action Plan for Missing Information "Use in Paediatric Individuals <16 Years of Age"

Objective of proposed actions	**a. ≥12 to ≤15 years of age:** C4591001 - Safety compared to placebo and immune-non-inferiority of neutralizing antibody immune response compared to subjects 16-25 years of age. b. **5 to <12 years of age:** C4591007 - Dose selection. Safety compared to placebo and immune-non-inferiority of neutralizing antibody immune response compared to subjects 18-25 years of age. Efficacy if sufficient cases accrue. c. **0 to <5 years of age**: - Dose selection. Safety compared to placebo and immune-non-inferiority of neutralizing antibody immune response compared to subjects 16-25 years of age. Efficacy if sufficient cases accrue.
Rationale for proposed actions	**≥12 to ≤15 years of age**: Need to collect evidence of safety and effectiveness to support immunization in this age group. **5 to<12 years of age**: Need to collect evidence of safety and effectiveness to support immunization in this age group. **0 to <5 years of age**: Need to collect evidence of safety and effectiveness to support immunization in this age group.

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Table 26. Action Plan for Missing Information "Use in Paediatric Individuals <16 Years of Age"

Monitoring by the sponsor for safety issue and proposed actions	**a. ≥12 to ≤15 years of age:** Study C4591001 - o Electronic diary for reactogenicity 7 days following each dose of vaccine. o Adverse events for one month after second dose. o Serious Adverse Events for 6 months after the second dose. o Related SAEs and related deaths for 24 months after the second dose. o Collection of COVID-19 and MIS-C cases up to 24 months after the second dose. b. **5 to <12 years of age:** Study C4591007 o Electronic diary for reactogenicity 7 days following each dose of vaccine. o Adverse events for one month after second dose. o Serious Adverse Events for 6 months after the second dose. o Related SAEs and related deaths for 24 months after the second dose. o Collection of COVID-19 and MIS-C cases up to 24 months after the second dose. c. **0 to <5 years of age**: Protocol number not yet assigned o Electronic diary for reactogenicity 7 days following each dose of vaccine. o Adverse events for one month after second dose. o Serious Adverse Events for 6 months after the second dose. o Related SAEs and related deaths for 24 months after the second dose. o Collection of COVID-19 and MIS-C cases up to 24 months after the second dose.

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Table 26. Action Plan for Missing Information "Use in Paediatric Individuals <16 Years of Age"

Milestones for evaluation and reporting	**a. ≥12 to ≤15 years of age:** Study C4591001 o Protocol (Amendment no. 7) submitted to BB-IND 19736 on: 07 October 2020. o First report with up to 1-month post dose 2 (safety): March 2021 o Further reports: o 6-month post dose 2 (safety): July 2021 o 24-month post dose 2 (safety): January 2023 b. **5 to <12 years of age:** Study C4591007 o Protocol submission: January 2021 (pending CBER feedback). o First report with up to 2-months post dose 2 (safety): September 2021. o Further reports: o 6-month post dose 2 (safety): March 2022. o 24-month post dose 2 (safety): September 2023. c. **0 to <5 years of age**: Protocol number not yet assigned. o Protocol submission: June 2021 o Study start planned by July 2021.

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3.1.4. Summary of Actions to be Completed, Including Milestones

Table 27. Summary of Safety Concerns and Action Plans

Safety Concerns	Ongoing/Planned Action	Summary of Objectives	Milestones	Due dates
Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)	a. Ongoing Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals (C4591001)	• The objective of the study is to evaluate the safety, tolerability, immunogenicity, and efficacy of Pfizer-BioNTech COVID-19 vaccine • An unfavorable imbalance between the vaccine and control groups in the frequency of COVID-19 disease, in particular for severe COVID-19 disease, may suggest the occurrence of vaccine-associated enhanced disease. Surveillance is planned for 2 years following Dose 2	Protocol submission:	22 April 2020 [a] (Initial version) 30 October 2020 (Amendment No. 9)
			CSR submission on completion of the first efficacy IA with 94 cases:	12 November 2020 [a]
			CSR submission on completion of full efficacy analysis with 164 cases:	November 2020
			CSR submission upon regulatory request:	Any time
			CSR submission 6 months post Dose 2:	December 2021
			Final CSR submission with supplemental follow-up:	August 2023
	b. Three post-authorization safety studies using active and passive surveillance strategies for safety events, including severe or atypical COVID-19, among individuals receiving Pfizer-BioNTech COVID-19 vaccine	• Assessment of occurrence of safety events, including severe or atypical COVID-19 disease in real-world use of Pfizer-BioNTech COVID-19 vaccine	Protocol draft submission:	November 2020
			Interim reports submission*:	31 March 2021 30 June 2021 31 December 2021 30 June 2022 31 December 2022
			Final CSR submission:	31 December 2023
			** Note: planned report dates assume vaccine availability on 01 December 2020*	

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Table 27. Summary of Safety Concerns and Action Plans

Safety Concerns	Ongoing/Planned Action	Summary of Objectives	Milestones	Due dates
Use in pregnancy and lactation	a. Planned clinical study to assess safety and immunogenicity in pregnant women who receive Pfizer-BioNTech COVID-19 vaccine.	Safety and immunogenicity of Pfizer-BioNTech COVID-19 vaccine in pregnant women.	Protocol submission:	February 2021
			Primary endpoints completion:	April 2023
	b. As feasible, monitor pregnancies exposed to the Pfizer-BioNTech COVID-19 vaccine, and as feasible, characterize use and outcomes in all of the planned post-authorization safety studies.	Monitor pregnancies exposed to the Pfizer-BioNTech COVID-19 vaccine, and as feasible, characterize use and outcomes.	Protocol draft submission:	November 2020
			Interim reports submission:	31 March 2021 30 June 2021 31 December 2021 30 June 2022 31 December 2022
			Final CSR submission:	31 December 2023
			Note: planned report dates assume vaccine availability on 01 December 2020	
Vaccine effectiveness	Non-interventional study (test-negative design) of individuals presenting with symptoms of potential COVID-19 illness in a real-world setting	Estimate the effectiveness of 2 doses of Pfizer-BioNTech COVID-19 vaccine against potential COVID-19 illness requiring admission to the ED or hospital where SARS-CoV-2 is identified.	Protocol submission:	Q1 2021
			Final CSR submission:	June 2023
	BNT162-01 cohort 13: Immunogenicity of Pfizer-BioNTech COVID-19 vaccine in immunocompromised subjects, including assessment of antibody responses and cell-mediated responses	To assess potentially protective immune responses in immunocompromised adults.	Protocol submission:	November 2020
			First IA submission:	Q3 2021

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Table 27. Summary of Safety Concerns and Action Plans

Safety Concerns	Ongoing/Planned Action	Summary of Objectives	Milestones	Due dates
Use in paediatric individuals <16 years of age	a. **≥12 to ≤15 years of age**: Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals (C4591001).	Safety compared to placebo and immune-non-inferiority of neutralizing antibody immune response compared to subjects 16-25 years of age.	Protocol (Amendment no. 7) submitted to BB-IND 19736	07 October 2020
			First report with up to 1-month post dose 2 (safety)	March 2021
			Report 6-month post dose 2 (safety)	July 2021
			Report 24-month post dose 2 (safety)	January 2023
	b. **5 to <12 years of age**: Phase 1 open label dose-finding study to evaluate safety, tolerability, and immunogenicity and phase 2/3 placebo-controlled, observer blinded safety, tolerability, immunogenicity, and efficacy study of a SARS-CoV-2 RNA vaccine candidate against COVID-19 in healthy children and adolescents ⩾5 to <18 years of age (C4591007).	Dose selection. Safety compared to placebo and immune-non-inferiority of neutralizing antibody immune response compared to subjects 18-25 years of age. Efficacy if sufficient cases accrue.	Protocol submission	January 2021 (pending CBER feedback)
			First report with up to 2-months post dose 2 (safety):	September 2021
			Report 6-month post dose 2 (safety):	March 2022
			Report 24-month post dose 2 (safety)	September 2023
	c. **0 to <5 years of age**: A phase 1 open label dose-finding study to evaluate	Dose selection. Safety compared to placebo and immune-non-inferiority of neutralizing antibody immune response	Protocol submission	June 2021

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Table 27. Summary of Safety Concerns and Action Plans

Safety Concerns	Ongoing/Planned Action	Summary of Objectives	Milestones	Due dates
	safety, tolerability, and immunogenicity and phase 2/3 placebo-controlled, observer blinded safety, tolerability, immunogenicity, and efficacy study of a SARS-CoV-2 RNA vaccine candidate against COVID-19 in healthy toddlers, infants and children 0 to <5 years of age (Protocol number not yet assigned).	compared to subjects 16-25 years of age. Efficacy if sufficient cases accrue.	Study start planned by:	July 2021

a. Indicates the effective date of submission.

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ANNEX

Pharmacovigilance Methods

BNT162b2 Vaccine: Pfizer-BioNTech COVID-19 Vaccine Data Capture Aid

3.1.5. Design and Conduct of Observational Studies

- EUA Safety Surveillance Study Plan: Attachment 1
- Post-authorization epidemiological safety studies: Attachment 2, Attachment 3, Attachment 4.

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